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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/865,993	05/25/2001	Brett P. Monia	RTS-0175	5849

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/865,993	MONIA ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 26 May 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): 112, second.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *please see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1,2,4-10 and 12-15*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *referrences cited.*

Attachment

The declaration under 37 CFR 1.132 filed 5-26-04 is insufficient to overcome the rejection of claims 1, 2, 4-10, 12-15, based upon 103 as set forth in the Office action mailed 1-27-04 because of the reasons elaborated in addressing Applicants' arguments below.

Applicants argue that no motivating force exists to impel persons of ordinary skill to use antisense for inhibiting DSP5 activity (e.g. as opposed to choosing peptides, proteins, antibodies or even small molecules instead to inactivate DUSP5), and that the specific motivation to utilize antisense for modulation of DSP5 was not provided in either the Sato or Ishibashi references. It is true that various avenues exist to inhibit the activity of a target protein. Antisense inhibition of a known target gene, however, is a routine approach utilized by one of ordinary skill to study the role of the target gene in a cellular process, aberration or cellular participation in a disease state. Applicants are correct that neither Sato nor Ishibashi explicitly disclose the inhibition of DUSP5 expression using antisense oligonucleotides. Both Sato and Ishibashi do, however, disclose the nucleotide sequence of the target DUSP5 gene from which antisense are derived and assessed for inhibitory capability using routine methods in the field of biochemistry and molecular biology - such as those techniques taught by Milner and Baracchini for inhibiting the expression of target gene of known nucleotide sequence in vitro. Sato and Ishibashi teach the motivation to study the role of DUSP5 expression in cell cycle progression and in cellular processes involved in atherosclerosis. The

teachings of Sato and Ishibashi, combined with the routine use of antisense oligonucleotides for inhibiting target gene expression, render the instant invention obvious to one of ordinary skill in the art of molecular biology (see Milner at 537, who teaches a combinatorial technique that allows simultaneous assessment of all possible oligonucleotides within a given region to identify sequences open to duplex formation and antisense inhibition of target gene expression: "...the arrays provide a simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence." And see examples 4 and 5, col. 17-18 of Baracchini for the use of cellular assays for the routine determination of antisense inhibitory activity), render the instant invention obvious. This disclosure, combined with the teachings of Milner in disclosing the routine empirical screening of antisense for their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537).

Applicants assert that an extremely low demonstration of success for identifying antisense compounds that would inhibit target polynucleotides is demonstrated in the teachings of Milner. Contrary to Applicants' assertions, the combinatorial technique taught by Milner allows for a simultaneous assessment of all possible oligonucleotides within a given region to inhibit target nucleic acid expression. The lack of correlation of predicted secondary mRNA structure with successful antisense inhibition was brought to light by the teachings of Milner, but this lack of correlation does not make the routine screening method for finding effective inhibitory antisense any less routine, it simply

warns that one cannot design antisense based simply on secondary structural predictions.

Applicants also assert that a subset of oligonucleotides tested either by Milner, or those provided in the oligonucleotide array disclosed in the instant declaration filed 5-26-04, suggest that a reasonable expectation of finding oligonucleotides able to inhibit target gene expression by at least 40% is low, and that finding successful oligonucleotides inhibiting target gene expression to this degree requires more than routine experimentation. It is unclear how these two examples provided in the declaration filed 5-26-04 (of antisense inhibition of two unrelated target genes, human tyrosine kinase, non-receptor and rat urate anion exchanger 1 mRNA) are generally representative of an expectation of success of antisense inhbition of target genes, especially in light of the myriad of target genes whose expression is known to be inhibited successfully using antisense (see Tables 12 & 14 from USPN 5,959,096, Tables 1 & 2 from USPN 5,959,097, Tables 1 & 2 from USPN 5,958,773, Table 2 from USPN 5,951,455, Table 14 from USPN 5,885,970, Tables 2 & 9 from USPN 5,877,309, Table 1 from USPN 6,046,320, Table 2 from USPN 5,962,671, Table 22 from USPN 6,133,246 and Tables 1 & 2 from USPN 6,063,626). The quantity of data existing in the scientific literature showing antisense inhibition to various target genes well illustrates that a reasonable expectation of success exists in finding antisense to target and inhibit a target gene of known sequence by at least 40%.

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